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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,746	09/09/2005	Navneet K. Ahluwalia	C1037.70035US01	2683

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

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06/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,746	AHLUWALIA ET AL.	
	Examiner	Art Unit	
	EMILY M. LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/01/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,64,65 and 72-79* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-14, 64 and 72-79* _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/09/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 15-63 and 66-71 are cancelled. Claims 76-79 are added. Claims 1-14, 64-65 and 72-79 are pending. Claims 6-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) a being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-5, 8-14, 64-65 and 72-79 are under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 8-14, 64 and 72-76 and 78-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the obviousness rejection, Applicant amended the claims with the following negative recitation: "and wherein the CpG immunostimulatory nucleic acid is not administered in combination with another nucleic acid of a different sequence".

Applicant submits that support for the cited recitation can be found throughout the specification, including for example, in the Examples, Figures and page 20, lines 1-2. Specifically, Applicant notes that the specification teaches the use of a single nucleic

acid species and the data show that a single nucleic acid species is effective in stimulating an immune response when contacted to cells.

Applicant's argument has been considered, however, it is not found persuasive. MPEP 2173.05(i) provides: Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.").

While the specification discloses the use of CpG immunostimulatory nucleic acids, the specification fails to properly exclude the **specific** use of another nucleic acid of a different sequence. In the instant case, the claims recite the transitional term, "having", which is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. Therefore, the presence of another nucleic acid of a different sequence is fully allowed by the claims and the specification. Additionally, the specification clearly discloses that the CpG immunostimulatory nucleic acid can be administered with other antiviral. The nucleic acid sequence taught by Witherell et al. is an antiviral agent.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-5, 8-14, 64 and 72-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Witherell et al.,[1] as evidenced by and in view of Hanecak el al.,[2] as evidenced by Kamal et al.[3]

In response to the rejection, Applicant amended the claims to exclude the administration of another nucleic acid of a different sequence than that of the CpG immunostimulatory nucleic acid.

Applicant's amendment has been considered, however, it is not entered in view of the written description rejection provided above.

Regarding claim 77, it is noted that Applicant has amended the claim with the recitation, "wherein the CpG immunostimulatory nucleic acid is not an antisense oligonucleotide". This amendment is noted, however, Hanecak et al. teaches an oligonucleotide that has the same structural requirements as Applicant's claimed oligonucleotide. The claims require the oligonucleotide to have a CpG motif. The specification discloses that the CpG motif contributes to the immunostimulatory activity of the oligonucleotide. In the instant case, the oligonucleotide of Hanecak et al. has the CpG motif. Thus, it would necessarily have the same immunostimulatory activity disclosed by Applicant. Thus, regardless of whether the oligonucleotide is called an antisense or immunostimulatory oligonucleotide, it is expected to and necessarily would have the same activity as it is structurally the same. Furthermore, MPEP 2112 (I)

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[1] Witherell et al. ISIS-14803 ISIS Pharmaceuticals. Current Opinion in Investigational Drugs, 2001, Vol. 2, No. 11, 1523-1529.
[2] Hanecak et al. Antisense oligonucleotide inhibition of hepatitis C virus gene expression in transformed hepatocytes. Journal of Virology, August 1996, Vol. 70, No. 8, 5203-5212.

provides: [T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

As presented in the previous office action, the claims are directed to a process comprising the administration of a CpG immunostimulatory oligonucleotide comprising the sequence of 5'$X_1X_2CGX_3X_43$', wherein X is any nucleotide and the oligonucleotide is 8-100 nucleotides long to a human subject having an HCV infection that was not successfully treated using previous non-CpG therapy. Claim 2, which depends on claim 1, specifies that the non-CpG therapy includes interferon-alpha. Claims 3-5, which depend on claim 2, specify that the non-CpG therapy includes interferon-alpha-2b, interferon-alpha-2a or consensus interferon-alpha; interferon-alpha and Ribavirin; and pegylated interferon-alpha and Ribavirin, respectively. Claim 8, which depends on claim 1, requires the oligonucleotide be a C class oligonucleotide. Claim 9, which depends on claim 1, requires the process to further comprise the step of administering interferon-alpha to the subject. Claim 10, which depends on claim 9, requires the interferon alpha be interferon-alpha-2b, interferon-alpha-2a or consensus interferon alpha. Claim 11, which depends on claim 9, requires that the interferon-alpha be administered substantially simultaneously with the oligonucleotide. Claim 12, which depends on claim 1, requires the oligonucleotide to comprise a backbone modification. Claim 13, which depends on claim 12, requires the backbone modification be a

[3] Kamal et al. Peginterferon alone or with ribavirin enhances HCV-specific CD4+ T-helper 1 responses in

phosphorothioate backbone modification. Claim 14, which depends on claim 1, requires the oligonucleotide to comprise a semi-soft backbone. Claim 64 is directed to the process of claim 1 with the addition of the administration of an antiviral agent requiring that the activity is independent of antisense activity. Claim 72, which depends on claim 8, requires that the oligonucleotide comprise a semi-soft backbone. Claims 73-75, which depend on claim 64, requires that the antiviral agent be interferon-alpha, ribavirin, and that the antiviral agent be administered substantially simultaneously with the oligonucleotide, respectively. Claim 76, which depends on claim 64, requires that the oligonucleotide have a semi-soft backbone. Claim 77 is directed to the method of claim 1, requiring that the CpG oligonucleotide is not an antisense oligonucleotide. Claims 78-79, which depends on claim 77, requires that the oligonucleotide be a C class immunostimulatory nucleic acid, and has a semi-soft backbone, respectively.

Witherell et al. teaches a process comprising the administration of ISIS-14803 to human subjects having an HCV infection that was not successfully treated using previous non-CpG therapy. The administration demonstrates that ISIS-14803 was effective in reducing HCV viral titer in said human subjects. Witherell et al. also discloses the use of ISIS-14803 as a single antiviral agent or in combination therapy with pegylated interferon and ribavirin in HCV infected subjects. [Clinical Development section, in particular.]

Witherell et al. also discloses while ISIS-14803 is effective in reducing HCV viral titer, it is unlikely that ISIS-14803 will be effective against HCV viruses. To overcome

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patients with chronic hepatitis C. Gastroenterology, October 05, 2002, Vol. 123, 1070-1083.

this limitation, Witherell et al. suggests the administration of ISIS-6095 with ISIS-14803. [Current Opinion section, in particular.] Witherell et al. notes that it is possible that the multiple inhibitory mechanisms activated by ISIS-14803 and ISIS-6095, it is possible that the combination of ISIS-14803 and ISIS-6095 would produce synergistic effects and delay the onset of resistance.

As evidenced by Hanecak et al., ISIS-6095 is a CpG containing oligonucleotide comprising the sequence of 5'X1X2CGX3X43', wherein X is any nucleotide and the oligonucleotide is 8-100 nucleotides long. ISIS-6095 comprises a phosphorothioate backbone modification.

In view of the suggestion made by Witherell et al., it would have been prima facie obvious for one of ordinary skill in the art to administer the CpG containing oligonucleotide known as ISIS-6095 with ISIS-14803 alone or in combination of interferon and ribavirin. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to reduce HCV viral titer in said HCV infected subjects. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because ISIS-6095 has proven to be effective at reducing HCV viral titer.

It is noted that Witherell et al. does not expressly suggest simultaneous or substantially simultaneous administration ISIS-6095 in combination with the other antiviral agents, including ISIS-14803, however, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to adjust the administration protocol, including simultaneous administration. One of ordinary skill in

the art, at the time the invention was made would have been motivated to do so to optimize the treatment. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the determination of a workable or optimal administration protocol is routinely practiced in the art.

Regarding claims 14 and 72, while ISIS-6095 is an oligonucleotide that comprises a phosphorothioate backbone, it should be noted that Hanecak et al. discloses that the backbone is a result effective variable. Hanecak et al. teaches that modification of the backbone varies the reduction in HCV viral titer and nuclease resistance. Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of ISIS-6095, including the use semi-soft backbones. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to vary the effectiveness of the HCV treatment and nuclease activity of the oligonucleotide. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the use of various and modified backbones is routinely practiced in the art.

Additionally, while it is not readily apparent from the disclosure of Witherell et al. whether the combination therapy of ISIS 14803 with pegylated interferon encompasses ineteferon-alpha-2b. However, as evidenced by Kamal et al. pegylated interferon is also PEG interferon alpha-2a. [Abstract, in particular.]

Conclusion

6. No claims are allowed. Claim 65 is free of the prior art.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./
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